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Dinuclear Zinc Catalyzed Asymmetric Spirannulation Reaction: An Umpolung Strategy for Formation of α-Alkylated-α-Hydroxyoxindoles

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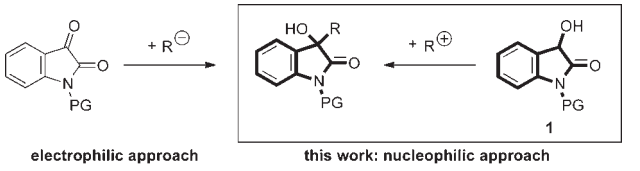
ABSTRACT

A highly diastereo- and enantioselective formal [3 + 2] cycloaddition of α,β-unsaturated esters and 3-hydroxyoxindoles catalyzed by a dinuclear zinc-ProPhenol complex is reported. The stereoselective Michael additions of 3-hydroxyoxindoles and the subsequent transesterifications afford spirocyclic δ-lactones.

Given that 3,3-disubstituted oxindoles are a common structural motif found in many natural products,[1] there has been an intense interest in the development of catalytic stereoselective methods for their preparation.[2] Of particular interest are processes that construct an oxygen-containing stereocenter at the 3-position. Kündig has reported the installation of such ethers and the corresponding amines via an intramolecular α-arylation[3] and has also demonstrated the synthesis of 3-hydroxyoxindoles via the intramolecular arylpalladation of ketoamides;[4] a subsequent report by Shibasaki and Kanai rendered this process enantioselective.[5] Lewis acid catalyzed hydroxylation of 3-substituted oxindoles using Davis's oxaziridine also gives access to this class of molecules,[6] as does the enantioselective addition of organometallic reagents,[7−10] enolates,[11]

Scheme 1. Nucleophilic Approach to α-Alkylated-α-Hydroxyoxindoles



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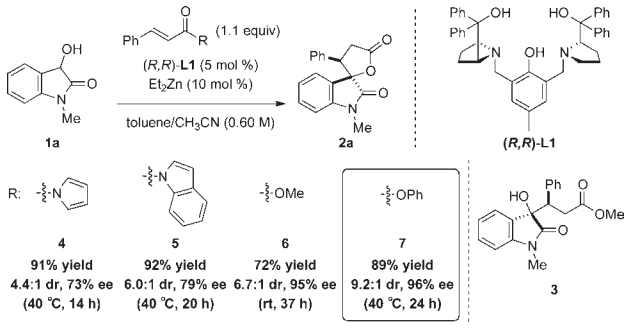
and electron-rich heterocycles to the corresponding isatins.[10a,12]

We wondered whether 3-hydroxyoxindole **1**, an isatinic anion equivalent, might undergo stereoselective addition to electrophiles to afford 3-hydroxy-3-alkyloxindoles via a formal umpolung[13] strategy, providing a new approach to highly functionalized 3-hydroxyoxindoles[14] (Scheme 1). Since the first synthesis of **1**[15] there have been only a few reports of its use in alkylation reactions.[16] Moreover, there are only a few direct catalytic highly enantioselective reactions using α-disubstituted α-oxycarbonyl compounds,[17] although the use of hydroxymethyl ketone derivatives have been well studied.[17e,f,18,19,20c] Herein we report a zinc-ProPhenol-catalyzed asymmetric tandem Michael addition−transesterification process that employs 3-hydroxyoxindoles as nucleophiles.

Scheme 2. Dinuclear Zinc-ProPhenol Complex-Catalyzed Tandem Michael Addition−Transesterification



Our studies commenced with the evaluation of several Michael acceptors for the desired process (Scheme 2).[20] Cinnamoylpyrrole (**4**) and the corresponding indole **5** were cleanly converted to spirocyclic oxindole **2a**[21] in excellent yields with moderate diastereo- and enantioselectivities. Attenuating the reactivity of the Michael acceptor by employing methyl cinnamate (**6**) significantly increased the enantioselectivity to 95% ee. In this case, open chain product **3** was also isolated in 19% yield and 97% ee as a single diastereomer. The corresponding phenyl ester based Michael acceptor **7** afforded **2a** exclusively in excellent yield, 9.2:1 dr, and 96% ee. Subsequent variation of the reaction temperature, solvent, metal, ligand, and substrate did not improve upon this initial lead (Table 1, entry 1). Lowering the reaction temperature to rt slightly decreased the diastereoselectivity without affecting the enantioselectivity (entry 2), but lowering the reaction concentration significantly decreased the diastereoselectivity (entry 3). The catalyst prepared in THF provided the desired product in comparable enantioselectivity, albeit in lower yield and diastereoselectivity (entry 4). When THF was employed as the solvent, **2a** was obtained in 98% ee but with modest diastereoselectivity (entry 5). The reaction was sluggish in toluene and dichloromethane, presumably due to poor solubility of **1a** in either of these solvents (entries 6 and 7). However, in both cases **1a** was obtained as a single diastereomer and with excellent enantioselectivity. The analogous dinuclear magnesium catalyst[22] furnished the desired product in only 51% ee and 2.3:1

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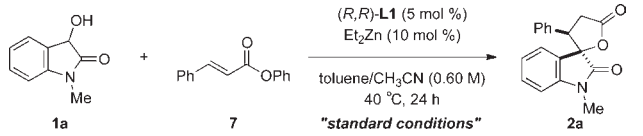
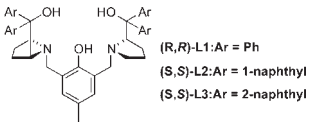
dr (entry 8). Replacing the phenyl substituents of the ligand with 1-naphthyl groups (**L2**) gave a racemic product with the reversed sense of diastereoselection (entry 9), whereas the ligand with 2-naphthyl groups (**L3**) provided **2a** in 95% ee but only 5.6:1 dr (entry 10). Interestingly, the *Z*-phenyl cinnamate gave **2a** in < 10% yield and with poor stereoselectivity (entry 11).

Table 1. Selected Optimization Experiments[a]



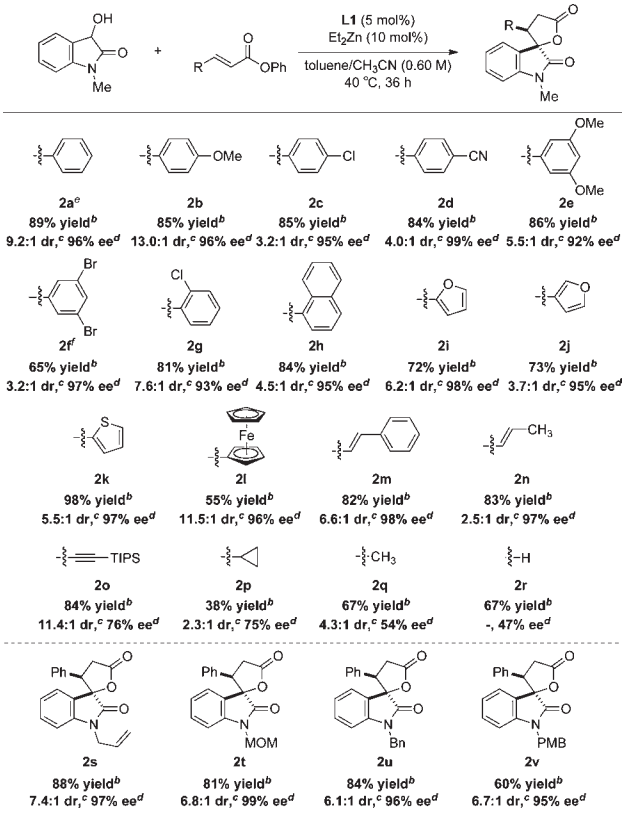
entry	variation from the standard conditions[b]	yield [%][c]	dr[d]	ee [%][e]
1	none	89	9.2:1	96
2	**rt** instead of 40 °C	(92)	8.5:1	96
3[f]	**0.35 M** instead of 0.60 M	(98)	4.4:1	94
4[f]	**THF** instead of toluene	(71)	4.7:1	94
5[f]	**THF** instead of CH_3CN	(94)	3.6:1	98
6[f]	**toluene** instead of CH_3CN	(20)	>19:1	94
7[f]	**CH_2Cl_2** instead of CH_3CN	(41)	>19:1	96
8[f]	**Bu_2Mg** instead of Et_2Zn	(54)	2.3:1	51
9[f]	**L2** instead of **L1**	(37)	1:1.8	0
10[f]	**L3** instead of **L1**	(86)	5.6:1	−95[g]
11	**(*Z*)-phenyl cinnamate** instead of **7**	8	1.1:1	39

[a] All reactions run on a 0.25 mmol scale. [b] The dinuclear zinc catalyst (0.0125 mmol, 5 mol %) prepared in toluene (0.13 mL) was injected to a mixture of (*E*)-cinnamaldehyde (0.25 mmol) and (*E*)-phenyl cinnamate (0.0127 mmol) in toluene (0.29 mL). The resulting mixture was stirred at 40 °C for 24 h. See Supporting Information for details. [c] Yields in parentheses were determined by ^{1}H NMR relative to mesitylene as an internal standard. [d] Determined by ^{1}H NMR of the crude mixture. [e] Determined by chiral HPLC analysis. [f] Reactions run at rt. [g] Opposite enantiomer.



With optimized conditions in hand, we evaluated the scope of this reaction (Scheme 3). Substitution at the C4-position of the aromatic group of the Michael acceptor is well-tolerated, although the level of diastereoinduction is somewhat dependent on its electronic properties (**2b**−**2d**). While the electron-donating 4-methoxy acceptor afforded **2b** with 13.0:1 dr and 95% ee, the electron-withdrawing 4-chloro- (inductive) and 4-cyano (mesomeric) acceptors gave the corresponding products with excellent ee but only modest diastereoinduction. The 3,5-dimethoxy and 3,5-dibromo substrates were converted to products **2e** and **2f**, respectively, with moderate dr's and high ee's. The absolute configuration was established unequivocally by single crystal X-ray analysis of **2f** to be (*R,R*) (Figure 1). *Ortho*-substitution of the aromatic ring is also possible (**2g** and **2h**). Acceptors containing heteroaromatic rings were obtained with excellent ee's (**2i**−**2k**), as was ferrocene-containing oxindole **2l**, although in the latter case the yield was modest, likely due to low solubility of the corresponding ester. Use of α,*β*,*γ*,*δ*-unsaturated esters yielded the 1,4-addition product exclusively, and the products were obtained with excellent ee's (**2m** and **2n**). An ynenoate can also be employed as an acceptor with a modest decrease in enantioinduction (**2o**). Alkyl substitution of the acceptor is also tolerated. The moderately sterically encumbered cyclopropyl group decreased the reaction conversion and **2p** was isolated in only 38% yield, but the smaller methyl group gave **2q** in 67% yield. Phenyl acrylate is also a competent substrate, providing unsubstituted *δ*-lactone **2r**. In addition to various acceptors, other nitrogen protecting groups on 3-hydroxyoxindole, such as allyl, methoxymethyl, benzyl, and *para*-methoxybenzyl, perform well in the desired reaction (**2s**−**2v**).

Scheme 3. Enantioselective Spirooxindole Formation[a]



[a] All reactions run on a 0.25 mmol scale. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC. [e] 24 h. [f] The absolute configuration was unambiguously determined to be (*R,R*) by the X-ray analysis. See Figure 1 and Supporting Information for details.

The catalyst is involved in both the Michael addition and the subsequent transesterification[23] (Scheme 4). When the racemic uncyclized methyl ester ***rac*-3** was subjected to the

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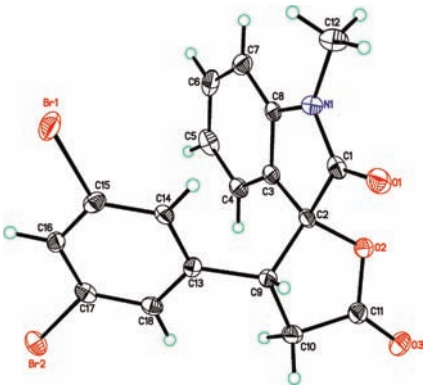
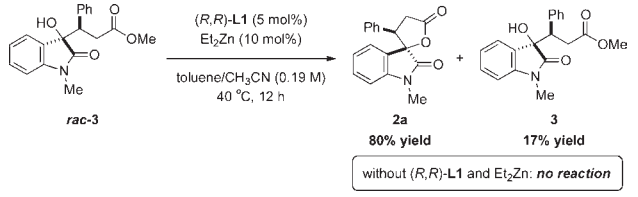


Figure 1. Single crystal X-ray diffraction analysis of **2f**.

reaction conditions, **2a** was obtained in 80% yield in the racemic form. The open-chained product **3** was isolated in 17% yield with 11% ee. This result indicates that the stereochemistry of **3** is not recognized by the catalyst during cyclization. Additionally, there might be the retro-Michael reaction−recombination process to induce some enantioselectivity. However, no formation of **2a** was observed in the absence of the dinuclear zinc ProPhenol complex.

Scheme 4. Zinc-ProPhenol Complex Is Necessary for the Transesterification

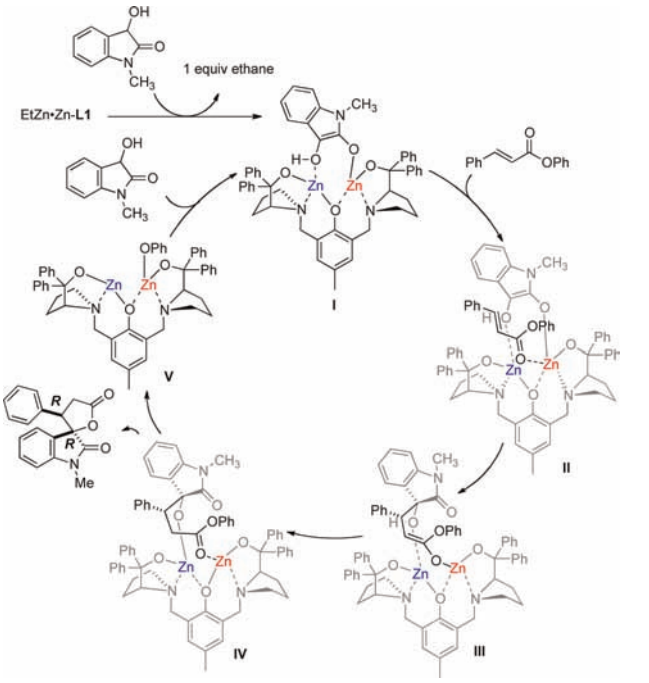


Our proposed catalytic cycle is described in Scheme 5. The first, 3-hydroxyoxindole is deprotonated by an ethylzinc species to give **I**. Phenyl cinnamate then coordinates the less hindered zinc atom (marked in red) to form **II**. C−C bond formation to **III** followed by tautomerization gives **IV**. This complex undergoes intramolecular transesterification to release the spirocyclic oxindole and regenerate the zinc phenoxide species that deprotonates another equivalent of 3-hydroxyoxindole.

In conclusion, we have developed a highly stereoselective synthesis of spirocyclic oxindoles via a dinuclear

(24) 3-Hydroxy-1-methylindolin-2-ones are sensitive to oxidation to form the corresponding isatins.

Scheme 5. Proposed Catalytic Cycle and Mode of Stereoinduction



zinc-ProPhenol-catalyzed tandem Michael addition−transesterification. This process represents a rare report of 3-hydroxyoxindoles as an isatinic anion equivalent in a catalytic enantioselective reaction, and the spirocyclic oxindole products are the highly versatile synthetic building block to provide various 3-alkyl-3-hydroxy-substitued oxindoles. This underutilized compound[24] provides a new way of synthesizing oxindoles bearing a tertiary alcohol at the stereogenic 3-position, and further efforts on this topic are currently underway and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization of the products, and crystallographic data (CIF) for **2f**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.